frontiers in Plant Science

MINI REVIEW
published: 22 March 2016
doi: 10.3389/fpls.2016.00356

Molecular Mechanisms for Vascular Development and Secondary Cell Wall Formation

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Vascular tissues are important for transporting water and nutrients throughout the plant and as physical support of upright growth. The primary constituents of vascular tissues, xylem, and phloem, are derived from the meristematic vascular procambium and cambium. Xylem cells develop secondary cell walls (SCWs) that form the largest part of plant lignocellulosic biomass that serve as a renewable feedstock for biofuel production. For the last decade, research on vascular development and SCW biosynthesis has seen rapid progress due to the importance of these processes to plant biology and to the biofuel industry. Plant hormones, transcriptional regulators and peptide signaling regulate procambium/cambium proliferation, vascular patterning, and xylem differentiation. Transcriptional regulatory pathways play a pivot role in SCW biosynthesis. Although most of these discoveries are derived from research in *Arabidopsis*, many genes have shown conserved functions in biofuel feedstock species. Here, we review the recent advances in our understanding of vascular development and SCW formation and discuss potential biotechnological uses.

Keywords: vascular, secondary cell wall, development, transcriptional regulation, *Arabidopsis*

Edited by:
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Specialty section:
This article was submitted to Plant Biotechnology, a section of the journal Frontiers in Plant Science

Received: *07 January 2016*
Accepted: *07 March 2016*
Published: *22 March 2016*

Citation:
Yang JH and Wang H (2016) Molecular Mechanisms for Vascular Development and Secondary Cell Wall Formation. Front. Plant Sci. 7:356. doi: 10.3389/fpls.2016.00356

INTRODUCTION

Plant vascular tissues are composed of xylem, phloem and the intervening procambial or cambial cells (Eames and MacDaniels, 1947). The proliferation of stem cells in the vascular meristem produces progeny cells, which either maintain their stem cell property or differentiate into xylem toward the center and phloem toward the periphery of plant stems (Elo et al., 2009; Miyashima et al., 2013; Jouannet et al., 2015). During the differentiation process, xylem fibers and tracheary elements (TEs), including vessels and tracheids, develop secondary cell walls (SCW; Ohashi-Ito and Fukuda, 2014). The development of TEs and xylary fibers undergoes a programed cell death (PCD) process (Schuetz et al., 2013). Compared to the thin primary cell walls, the SCW is much thicker and accounts for the majority of cellulosic biomass that serves as a renewable resource for biofuel production (Demura and Ye, 2010; Carpita, 2012).

Our understanding of vascular development including hormonal response, peptide signaling, and transcriptional regulation has advanced significantly since the publication of a few recent reviews (Kondo et al., 2014b; Ruzicka et al., 2015). Rapid progress have also been made in the genetic regulation of SCW biosynthesis due to the growing interest in clean bioenergy and biofuels (Somerville, 2007; Carroll and Somerville, 2009; Pauly and Keegstra, 2010). In fact, vascular development and SCW formation are closely related biological processes that can be regulated by the same signaling pathway (Ito et al., 2006; Etchells and Turner, 2010). In this mini-review, we focus on progress in elucidating the regulatory pathways involved in vascular development, xylem differentiation and SCW deposition.

THE INITIATION OF VASCULAR PROCAMBIUM

Plant stems contain most of the collectable terrestrial biomass, but the study of vascular procambium initiation in the stem is impeded because these cells are imbedded under layers of other tissues and are difficult to access. Most of the current knowledge on procambium initiation and regulation is derived from studies in embryos, root apical meristems, and leaf venation systems. Some of the genes and signaling pathways, such as the Class III homeodomain leucine zipper (HD-ZIP III) and the CLAVATA 3 (CLV3)/EMBRYO SURROUNDING REGION (ESR) related (CLE) signaling pathway, function in multiple tissues, and therefore appear to be more broadly involved in probambium development in general (Zhang et al., 2014; Ruzicka et al., 2015). The vascular procambium develops during embryogenesis and determines vascular patterning in postembryonic growth. In early globular embryos, division of the four inner cells generates procambial/provascular initials (Hardtke and Berleth, 1998; Berleth et al., 2000; Jouannet et al., 2015). These initial cells further divide periclinally, increase in number and form the first vascular strands in a pattern similar to what is later observed in young seedlings. During postembryonic development, the initiation of procambial strands in leaf primordia and root meristems are extensively studied and reviewed elsewhere (Cano-Delgado et al., 2010; Kondo et al., 2014b; Jouannet et al., 2015; Ruzicka et al., 2015).

The plant hormone auxin, mainly indole acetic acid (IAA), regulates the initiation of vascular procambial cells. Mutation of the auxin responsive transcription factor (TF) *AUXIN RESPONSE FACTOR 5* (*ARF5*)/*monopteros* (*MP*) inhibits vascular procambial cell formation in embryos (Hardtke and Berleth, 1998) (**Figure 1A**). The expression of *ARF5/MP* is restricted to the provascular initials (Hamann et al., 2002). Furthermore, the expression of *ARF5/MP* is upregulated in the developing procambium cells and is preceded by auxin accumulation (Hardtke and Berleth, 1998). ARF5/MP binds to the promoter of *ARABIDOPSIS THALINA HOMEOBOX 8* (*ATHB8*) and directly regulate its expression through an auxin responsible element (ARE, TGTCTG; Donner et al., 2009). In addition to auxin signaling, auxin transport is also important to procambium development. During embryogenesis, the auxin efflux carrier PIN-FORMED1 (PIN1) protein is polarly localized in the inner cells of the pre-procambium (Friml, 2003). The expression level of *PIN1* is dramatically reduced in *mp* mutant plants (Wenzel et al., 2007), suggesting that MP may regulate *PIN1* at the transcriptional level (**Figure 1A**). TARGET OF MONOPTEROS 5 (TMO5), a basic helix-loop-helix (bHLH) TF, is identified as a direct target of ARF5/MP. TMO5 is expressed in procambium initials in globular stage embryos, and is restricted to the xylem precursor cells in the postembryonic root (Schlereth et al., 2010). TMO5 physically interacts with another bHLH TF LONESOME HIGHWAY (LHW) to control the periclinal divisions (De Rybel et al., 2013; Ohashi-Ito et al., 2013). Ectopic expression of TMO5 and LHW causes periclinal cell divisions in other tissues, indicating conserved functions of the TMO5/LHW dimer (De Rybel et al., 2013).

Cytokinin (CK) is another major plant hormone that is critical to procambium initiation. The direct downstream target of TMO5/LHW dimer was identified as LOG4 (**Figure 1A**), a rate-limiting enzyme in CK biosynthesis (De Rybel et al., 2014; Ohashi-Ito et al., 2014). In the *Arabidopsis* root procambium, CK

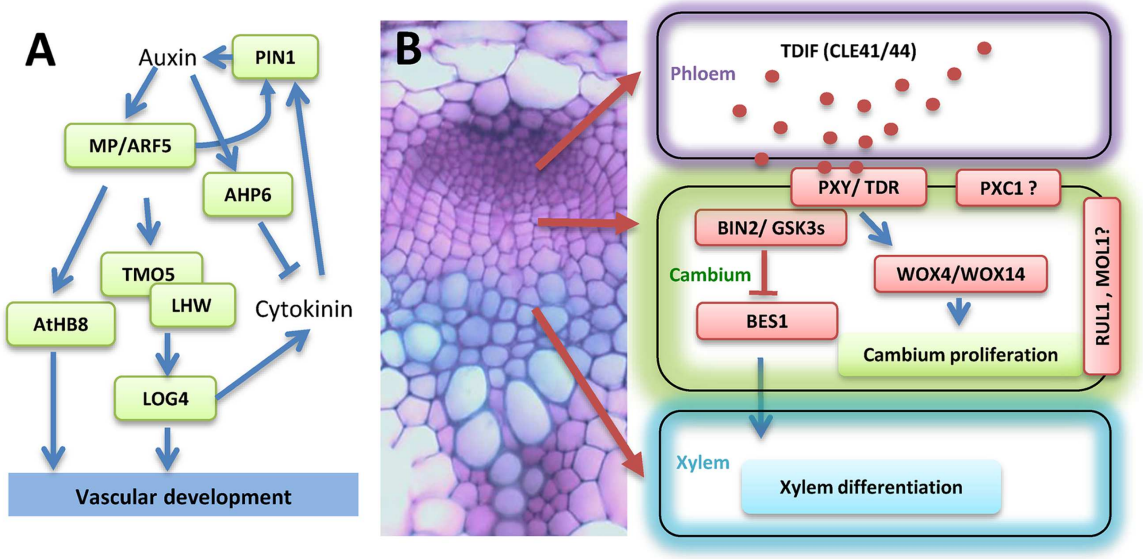

FIGURE 1 | Illustration of the transcriptional and hormonal regulation of vascular development. (A) Hormonal and transcriptional control of vascular procambium initiation. **(B)** Regulation of vascular procambium proliferation, xylem differentiation, and vascular patterning by peptide TDIF (red dots in the phloem) signaling. A cross section of the *Arabidopsis* stem to demonstrate cell types is shown on the left. The localization of different components of the TDIF signaling pathways is illustrated on the right. Abbreviations for gene names are specified in the text.

promotes the bisymmetric distribution of PIN1 and PIN7, and as a result, channels auxin toward the axis of xylem precursor cells. In contrast, auxin positively regulates the expression of an inhibitor of CK signaling, *AHP6* (**Figure 1**). This mutually inhibitory feedback loop between auxin and CK sets distinct boundaries and defines the organization of the root vascular cylinder (Bishopp et al., 2011). In addition to auxin and CK, other hormones may also play a role in procambium initiation (Jouannet et al., 2015; Ruzicka et al., 2015). The aforementioned hormonal regulations were derived from studies in embryos and roots. It would be interesting to investigate how perturbation of these pathways affect procambium and cambium development in stems.

THE DEVELOPMENT OF VASCULAR TISSUES IN THE *Arabidopsis* STEM

The Development and Patterning of the Vascular Bundle

Vascular bundles of the *Arabidopsis* stem are organized in a collateral pattern with the procambium located between xylem and phloem tissues. During secondary growth, vascular cambia develop in both fascicular (vascular bundles) and interfascicular regions and form a continuous ring, during which process auxin plays a critical role (Mazur et al., 2014). Class III homeodomain leucine zipper (HD-ZIP III) genes, i.e., *ATHB8, PHABULOSA (PHB), PHAVOLUTA (PHV), REVOLUTA (REV),* and *ATHB15,* regulate vascular tissue development and adaxial-abaxial patterning in *Arabidopsis*. These genes are shown to be induced by auxin (Donner et al., 2009; Ursache et al., 2014). These HD-ZIP III TFs promote adaxialization and cause the formation of amphivasal bundles (phloem surrounded by xylem) in gain of function mutants (McConnell et al., 2001). In contrast, amphicribral vasculature (xylem surrounded by phloem) were observed in loss of function mutants of HD-ZIP III genes, such as in the triple mutant of *phb phv rev* (Emery et al., 2003). The function of AtHB15 may be different from its family members, especially REV. The triple mutant *phb phv athb15* develops amphivasal vasculature that is opposite to the *phb phv rev* (Green et al., 2005; Prigge et al., 2005). The expression of *HD-ZIP III* TFs is regulated by micro-RNA 165/166 (*miR165/166*). Activation tagging of *miR165b*, *miR166a,* and *miR166g* promote the cleavage of the transcripts of *PHB*, *PHV,* and *AtHB15* resulting in internalized amphivasal bundles (Kim et al., 2005; Williams et al., 2005; Du et al., 2015). The transcripts of *REV* and *ATHB8* are less affected by activation tagging of miR165/166 due to unknown mechanisms (Du and Wang, 2015).

The Proliferation and Maintenance of Vascular Procambium

The proliferation of vascular procambium and subsequently xylem differentiation is regulated by a CLE peptide signaling. In *Arabidopsis*, *CLE41* and *CLE44* encode the dodeca-peptide TE differentiation inhibition factor (TDIF), which activity was originally identified from a *Zinnia* cell culture system (Ito et al., 2006). TDIF is synthesized in the phloem, diffuses into the cambial tissue, and binds to its receptor, a leucine-rich repeat receptor like kinase (LRR-RLKs) named PHLOEM INTERCALATED WITH XYLEM (PXY; Ito et al., 2006; Fisher and Turner, 2007; Hirakawa et al., 2008). TDIF signaling activates the expression of *WUSCHEL-RELATED HOMEOBOX 4* (*WOX4*) and *WOX14*, resulting in the promotion of cambial cell proliferation (Hirakawa et al., 2010; Etchells et al., 2013) (**Figure 1B**). Mutation of *WOX4* represses procambium proliferation in the hypocotyl of 7-day-old seedlings (Hirakawa et al., 2010; Etchells et al., 2013). However, overexpression of *WOX4* does not significantly increase procambial cell proliferation in *Arabidopsis* hypocotyls (Hirakawa et al., 2010). It is possible that other factors, such as HAIRY MERISTEM (HAM; Zhou et al., 2015), are required for WOX4 function. HAM family TFs act as conserved interacting cofactors with WOX proteins and may be essential for all stem cell niches in plant (Zhou et al., 2015). The TDIF peptide also regulates vascular tissue organization as overexpression of *CLE41* or *CLE44* with a ubiquitous promoter or a xylem specific promoter leads to a loss of cell division orientation (Etchells and Turner, 2010). Three other LRR-RLKs, *PXY-CORRELATED 1* (*PXC1*), MORE LATERAL GROWTH 1 (MOL1) and REDUCED IN LATERAL GROWTH 1 (RUL1) were shown to be involved in regulating cambium activity (Agusti et al., 2011; Wang et al., 2013). Further analysis of these receptor like kinases may help to better understand the maintenance of procambial and cambium cells (**Figure 1B**).

The Differentiation of Xylem Cells

The mechanism of how TDIF-TDR signaling represses xylem differentiation was revealed recently. BRASSINOSTEROID-INSENSITIVE 2 (BIN2) was identified as an interacting partner of TDR/PXY in a yeast two-hybrid screening (Kondo et al., 2014a). BIN2 is a Glycogen Synthase Kinase 3 (GSK3) protein and is directly associated with TDR/PXY at the plasma membrane. BES1 (BRI-EMS-SUPPRESSOR 1) is one of the BIN2 downstream TFs in the brassinosteroid (BR) signaling pathway (Li and Nam, 2002; Yin et al., 2002), and positively regulates xylem cell differentiation (Kondo et al., 2015). TDIF binding to its receptor TDR/PXY disassociates BIN2 from the complex, suppresses the function of BES1, and subsequently inhibits xylem formation (Kondo et al., 2014a).

TRANSCRIPTIONAL REGULATION OF SCW DEVELOPMENT

Secondary cell wall deposition is regulated by a large number of TFs through both hierarchical and non-hierarchical regulatory networks (Wang and Dixon, 2012; Zhong and Ye, 2015). At least three layers of regulators, including NAC (NO APICAL MERISTEM, ATAF1, ATAF2, and CUP-SHAPED COTYLEDON 2) domain master regulators in tier 3, two MYB domain regulators in tier 2 and many other regulators in tier 1, are directly involved in regulating SCW biosynthetic genes (**Figure 2**).

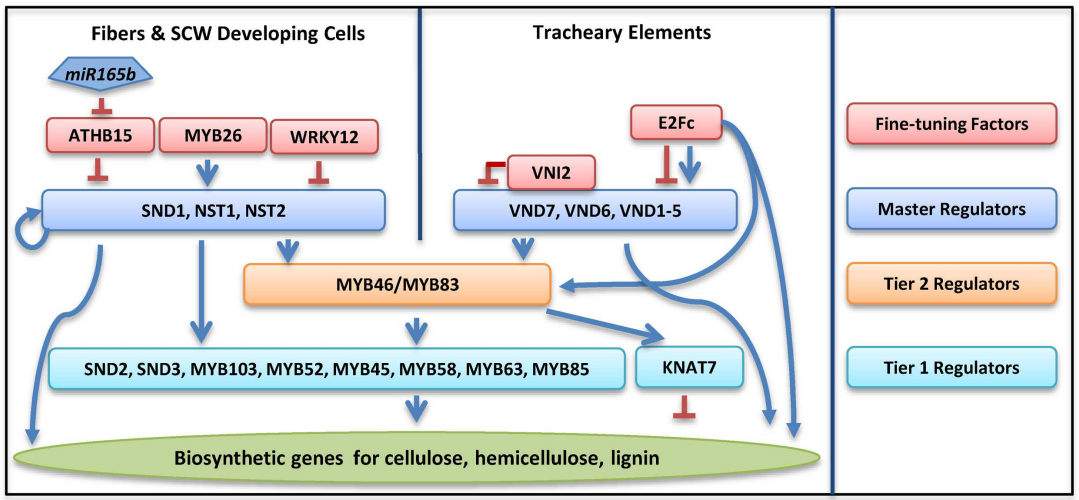

FIGURE 2 | Transcriptional regulatory networks in regulating secondary cell wall biosynthesis in *Arabidopsis thaliana*. Colored rectangles represent transcription factors in different tiers as specified in the column on the right. Blue arrows denote positive regulation, while a red line with blunt ends denotes negative regulation.

The NAC Domain (Tier 3) Master Regulators

Three NAC domain TFs are defined as master regulators for their function in regulating all three components, i.e., cellulose, hemicellulose, and lignin biosynthesis in xylary fibers (Wang et al., 2011; Wang and Dixon, 2012; Zhong and Ye, 2015). These three NACs are *NAC SECONDARY WALL THICKENING PROMOTING FACTOR 1* (*NST1*), *NST2,* and *NST3/SECONDARY WALL-ASSOCIATED NAC DOMAIN PROTEIN 1* (*SND1*; Zhong et al., 2006, 2007b; Mitsuda et al., 2007). The SCW deposition is disturbed in the vascular and interfascicular fibers of the *nst1nst3* double knockout plants, while ectopic overexpression of *NST1* or *SND1* leads to ectopic SCW formation in a variety of tissues (Zhong et al., 2006, 2007b; Mitsuda et al., 2007). In *Arabidopsis* anther endothecium, secondary wall thickening is controlled by NST1 and NST2 (Mitsuda et al., 2005). In xylem vessels, VASCULAR-RELATED NAC DOMAIN (VND) proteins regulate both SCW biosynthesis and PCD (Yamaguchi et al., 2010a). VND6 and VND7 positively regulate xylem vessel differentiation (Kubo et al., 2005). In *Arabidopsis*, ectopic expression of *VND6* and *VND7* triggers metaxylem and protoxylem formation, respectively (Kubo et al., 2005; Yamaguchi et al., 2010a). VND6 and VND7 activate the expression of a broad range of genes involved in PCD, such as xylem-specific papain-like cysteine peptidase (XCP1; Funk et al., 2002; Yamaguchi et al., 2011). Other VND family members, i.e., VND1 to VND5, function redundantly with VND6 and VND7 in vessel development (Zhou et al., 2014).

The MYB Domain Second Level (Tier 2) Regulators

MYB46 and MYB83 are the second level regulators downstream of the NAC domain master regulators (Zhong et al., 2007a; Zhong and Ye, 2012). SND1 directly binds to the promoter of MYB46 and activates its expression (Zhong et al., 2007a; Wang et al., 2011). Overexpression of *MYB46* or *MYB83* leads to over-accumulation of all three major SCW components, indicating that both of these MYBs also function as master switches (Zhong et al., 2007a; Zhong and Ye, 2012). These MYBs are also direct targets for VND6 and VND7 (Ohashi-Ito et al., 2010; Yamaguchi et al., 2011), indicating that they are important for SCW formation in both vessels and xylary fibers. Consistent with this observation, simultaneous knockout of *MYB46* and *MYB83* results in a more severe phenotype than those observed from the *nst1nst3* double mutant (Zhong and Ye, 2012).

Other Regulators (Tier 1) for SCW Biosynthesis

Many other TFs function downstream the NAC and MYB domain master regulators (Zhong et al., 2008; Ko et al., 2009). Among these regulators, *SND2*, *SND3,* and *MYB103*, are able to induce the expression of cellulosic synthesis genes and increase SCW thickening in fibers (Zhong et al., 2008; Hussey et al., 2011). Repression of these three genes, as well as three other MYB TFs, *MYB52*, *MYB54,* and *MYB85* reduced cell wall thickness, supporting the idea that these genes are positive regulators for SCW synthesis (Zhong et al., 2008). Overexpression of *MYB52* and *MYB54* upregulate the expression of *CELLULOSE SYNTHASE 8* (*CesA8*), *IRREGULAR XYLEM 9* (*IRX9*), and 4-*COUMARATE-COA LIGASE* (*4CL*), genes responsible for the synthesis of cellulose, hemicellulose, and lignin, respectively (Zhong et al., 2008). Three MYB TFs, MYB58, MYB63, and MYB85, have been suggested to directly regulate lignin biosynthesis in *Arabidopsis* (Zhong et al., 2008; Zhou et al., 2009). Many regulators in tier 1 are positively regulated by both tier 3 master regulators and tier 2 regulators (Zhong et al., 2008; Ko et al., 2009; Kim et al., 2014; Zhong and Ye, 2014).

Fine-Tuning of the SCW Regulatory Network

There are some TFs that do not appear to easily fit into SCW-related regulatory networks, which are primarily under feed forward regulation (Taylor-Teeples et al., 2015). *KNOTTED ARABIDOPSIS THALIANA7* (*KNAT7*) is identified as a negative regulator of SCW synthesis. In the *knat7* knockout mutant, irregular xylem vessel formation was observed, but the interfascicular fibers developed thicker SCW (Li et al., 2012). *KANT7* is induced by overexpression of *MYB85* and several NAC master regulators (Zhong et al., 2008). The mechanism of *KANT7* in regulating SCW biosynthesis is still unclear. Another TF *XYLEM NAC DOMAIN 1* (*XND1*) regulates SCW deposition and PCD in xylem, but it is not clear how this gene interacts with other members in regulatory pathways (Zhao et al., 2008). Three MYB TFs, MYB4, MYB7, and MYB32, are negative regulators for the NAC domain master regulators, while the expression of these three MYB genes are positively regulated by the tier2 master regulator MYB46 (Zhong et al., 2008; Ko et al., 2009; Wang and Dixon, 2012; Zhang et al., 2014). These negative regulators may be important to SCW synthesis by providing flexibility under undesirable growth conditions (Jin et al., 2000).

Several regulators have been shown to negatively regulate the NAC domain master regulators. *VND INTERACTING 2* (*VNI2*) directly binds to the VND7 protein, and represses *VND7* expression (Yamaguchi et al., 2010b). Overexpression of *VNI2* leads to failure of xylem vessel development due to inhibition of *VND7*, while mutation of *VNI2* upregulates genes involved in vessel formation (Yamaguchi et al., 2010b). WRKY12 is a negative regulator of the NAC domain regulator NST2 (Wang et al., 2010). In wild-type plants, WRKY12 binds directly to the promoter of *NST2*, resulting in the suppression of SCW biosynthetic genes in pith cells (Wang et al., 2010). Mutation of *WRKY12* de-represses SCW biosynthesis in the pith cells, resulting in a SCW thickening in pith (STP) phenotype (Wang et al., 2010).

Positive regulators have also been identified in regulating NAC domain master regulators. Overexpression of *MYB26* leads to enhanced SCW deposition. Further analysis indicated that MYB26 positively regulate SCW accumulation through NST1 and NST2 (Yang et al., 2007). Recently, a large scale of Yeast one Hybrid (Y1H) screen identified another upstream TF, E2Fc, from the SCW regulatory network. E2Fc can directly bind the promoters of *VND6* and *VND7*, and may function as a positive or negative regulator depends on their relative concentration (Taylor-Teeples et al., 2015).

BIOTECHNOLOGICAL UTILIZATION OF DISCOVERIES FROM MODEL SPECIES

The *Arabidopsis* stem and hypocotyl undergo secondary growth that resembles perennial trees, which makes it a model plant for studying vascular development and wood formation (Chaffey et al., 2002; Nieminen et al., 2004). Indeed, most of the current knowledge of vascular development and xylem differentiation are derived from studies in *Arabidopsis*, or more recently, from a monocot model species *Brachypodium* (Handakumbura and Hazen, 2012). Some of the regulatory genes identified from model plants have conserved functions in biofuel feedstocks (Shen et al., 2009; Zhong et al., 2011). For example, TDIF signaling controls cambial cell divisions in aspen. Precise tissue specific overexpression of the aspen receptor kinase PttPXY and its peptide ligand PttCLE41 exhibited a dramatically increase in tree growth and productivity (Etchells et al., 2015). In another study, significant enhancements in forage biomass and quality were achieved through engineering WRKY TFs in *Zea mays*, *Panicum virgatum,* and *Medicago sativa* (Gallego-Giraldo et al., 2016). The biotechnological utilizations of genes discovered from fundamental research in vascular development and SCW synthesis provide proof of concept for future bioengineering of biofuel feedstocks.

CONCLUDING REMARKS

We discuss the advances in the molecular regulation of vascular development and SCW deposition. Multiple regulatory pathways, such as plant hormones, HD-ZIP III TFs, VND TFs and CLE peptide signaling, have been suggested in regulating procambium development and xylem differentiation. Future studies should focus on the interactions among these pathways. For SCW biosynthesis, NAC domain TFs, MYB domain TFs and many other TFs are members of the gene regulatory network. Even though both positive and negative feedback regulation have been proposed, we know little about the molecular mechanisms of how xylem cells become committed to their identity. In order to fully understand these processes, it is essential to identify novel genes responsible for cambial cell division and xylem differentiation.

AUTHOR CONTRIBUTIONS

JY and HW prepared the figures, wrote the manuscript, read and approved the final version.

FUNDING

This work was supported by National Science Foundation (IOS-1453048), and in part, by USDA NIFA Hatch project #CONS00925 to HW.

ACKNOWLEDGMENTS

We thank Drs. Richard McAvoy and Karl Guillard for critical reading of the manuscript. We apologize to those authors whose important contribution has not been discussed in this article due to space limitations.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.